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10/556,937	10/31/2006	Michael R. Costa	EX04-044C-US	6980

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EXAMINER	
GEBREYESUS, KACNEW H	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/556,937	COSTA ET AL.	
	Examiner	Art Unit	
	KAGNEW H. GEBREYESUS	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 17-28* is/are pending in the application.

4a) Of the above claim(s) *2-7,13-15 and 20-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 8-12, 17-19, 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election on September 23, 2009 with traverse of group V comprising claims 1, 8-12, 17-19, 26-28 and the polynucleotide of SEQ ID NO: 5 in reply to the restriction requirement mailed on March 23, 2009 is acknowledged. Claims 1-15, 17-28 are pending. Claim 16 is cancelled. Claims 1 and 26 are amended. Claims 2-7, 13-15, 20-25 are withdrawn from consideration as being directed to claims that belong to a non-elected group. See 37 CFR 1.142(b) and MPEP § 821.03.

Because Applicants did not specify the reason why the restriction requirement was improper, the restriction requirement will be regarded as an election without traverse and the requirements are made final. Claims 1, 8-12, 17-19, 26-28 and the elected polynucleotide species of SEQ ID NO: 5 are present for examination.

The following rejections are initiated by amendment to the claims.

The following 35 U.S.C. 112, first paragraph rejection is based on the recitation of fragments OR derivatives thereof in independent claims 1 and 26.

Maintained - Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 8-12, 17-19, 26-28 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s)

contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue:

"...First, Applicants point out that they are claiming a novel method of using MARK polynucleotides and not the polynucleotides themselves, which polynucleotides are published and known in the art. Second, the specification describes, among other things, the structure, physical and chemical properties, functional characteristics, and methods of making the recited MARK nucleic acid molecules. In addition, the specification provides a sufficient number of representative examples of MARK species. Applicants' disclosure, in combination with MARK polynucleotides known and described in the art, is sufficient to satisfy the written description requirement. Nevertheless, solely in an effort to advance prosecution, claim 1 has been amended to recite a MARK nucleic acid comprising any of SEQ ID NOs: 1-13 or a functionally active fragment thereof, wherein the fragment has kinase activity..."

However the amendments to the claims now recite "fragments or derivatives with kinase activity" which can encompass any kinase with any sequence or function. Furthermore the specification describes examples of SEQ ID NO: 5, 8 and 10 nucleic acids encoding kinases in the assay system. However these sequences are not representatives for the diversity of polynucleotides envisaged to be used in the claimed method because common characterizing features of these fragments and derivative of the polynucleotide of SEQ ID NO: 5 with any kinase function are not provided in the specification.

Thus the specification does not clearly convey the information that applicants have invented the subject matter which is claimed because other than the polynucleotide of SEQ ID NO: 5, 8 and 10 Applicants have not put the public in

possession of what the applicant broadly claim as their invention.

These claims are still directed to a method of identifying an agent that modulates PTEN pathway comprising an assay that uses a genus of nucleic acids encoding a kinase activity. The specification describes the structure of a few polynucleotides encoding MARK kinases, SEQ ID NO: 5 comprising 4726 nucleotides, SEQ ID NO: 8 comprising 1725 nucleotides or SEQ ID NO: 10 with 4919 nucleotides respectively. However, the specification does not describe an identifying characteristic or property for the structure of all possible derivative of MARK polynucleotides that encodes any kinase. The specification does not teach using any MARK polynucleotide with any structure in the assay system to identify a candidate PTEN pathway modulating agent.

The Federal Circuit has pointed out that under United States law, a description that does not render a claimed invention obvious cannot sufficiently describe the invention for the purposes of the written description requirement of 35 U.S.C. 112. Eli Lilly, 119 F.3d at 1567, 43 USPQ2d at 1405. Compare Fonar Corp. v. General Electric Co., 107 F.3d 1543, 1549, 41 USPQ2d 1801, 1805 (Fed. Cir. 1997).

To satisfy the written description requirement for the claimed genus of MARK polynucleotides to be used in the assay system, a sufficient description of a representative number of species by actual reduction to practice, or by a disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics,

sufficient to show the applicant was in possession of the claimed genus must be provided (*See Eli Lilly,119 F.3d at 1568, 43 USPQ2d at 1406).*

In the instant case, the skilled artisan cannot envision the detailed chemical structure of a genus of polynucleotides comprising all fragments and derivatives of SEQ ID NO: 5 that are encompassed in the claimed method.

Furthermore Applicants argue:

"...With respect to the Office's comment that the specification does not describe how the function of a defective PTEN can be overcome by expressing a recombinant polynucleotide encoding a MARK, Applicants submit that the specification teaches at pages 25 and 33 that defective PTEN results from the over-expression, under-expression, or mis-expression of PTEN..."

Applicant's argument regarding the nexus between MARK kinase and the PTEN pathway has been considered but not found persuasive. This is because while the possible link between specific MARK polynucleotides are taught in the specification, a link between any fragment or derivative of a polynucleotide of SEQ ID NO: 5 is not discussed.

Thus the specification lacks description for a method broadly encompassing the use of any fragment or derivative which encodes a polypeptide with kinase activity the specification fails to describe the claimed invention in a clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

The rejection under 35 U.S.C. 102(b) is withdrawn. However the following rejection applies.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 8-12, 17, 18, 26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drew et al (MARK, a Novel Family of Protein Kinases That Phosphorylate a Microtubule Associated protein and Trigger Microtubule Disruption Cell vol. 89, 297-308, 1997 in IDS) in view of Martinez et al (Synthetic small inhibiting RNAs: efficient tools to inactivate oncogenic mutations and restore p53 pathways. *Proc. Natl Acad. Sci. USA*, 99, 14849–14854 (2002)) further in view of Arora et al (PHOSPHORODIAMIDATE MORPHOLINO ANTISENSE OLIGOMERS INHIBIT EXPRESSION OF HUMAN CYTOCHROME P450 3A4 AND ALTER SELECTED DRUG METABOLISM Drug metabolism and disposition Vol. 30, No. 7 page 757-762).

Drew et al teach that MARK phosphorylates MAP2, MAP4 and causes their dissociation from microtubules and results in increased microtubule dynamics which results in disruption of microtubule arrays leading to morphological changes of cells and cell death in the case of MAP 2. Furthermore they teach that MARK phosphorylates the neuronal MAP kinase tau and prevents tau from binding to microtubules. This results in aggregation of tau proteins (deposits) which is the main constituent of paired helical filaments in the neurofibrillary tangles in Alzheimer's. The accumulation of these deposits in brain is related to progression of dementia (see column 1, discussion). Furthermore Drew et al teach the activity of MARK depends on phosphorylation of MAPs at the KXGS motif (position 262 in the tau protein). Drew et al also teach that disruption of microtubules caused by phosphorylation of MAP can be prevented by an agent known as taxotere (see page 303 1st paragraph). Furthermore Drew et al teach that protein phosphatase 2A (PP2A) degrades MARK and prevents MARK activity as seen by cell morphology and cell survival assays.

To demonstrate the above, Drew et al teach an assay wherein CHO cells were transformed with a vector comprising a polynucleotide that encodes MARK 1 (GenBank accession number Z83868) or MARK 2 (accession number Z83869), and a vector expressing MAP2c (thus test agents) or in the presence or absence of taxotere (an agent that stabilizes microtubules).

In both of the above assays, differential phenotypes of CHO cells were seen (see Drew et al page 303, fig. 5). Thus it would have been obvious to an ordinary person skilled in the art to search for an agent that interferes with the activation of MARK in

view of preventing its ability to phosphorylate MAP kinases such as the neuronal MAP kinase tau because of the deleterious effects recited above.

Drew et al do not teach using nucleic acid modulators such as anti-sense, RNAi or PMO in an assay.

Martinez et al teach siRNAs may be used to suppress expression of point-mutated genes and provide the basis for selective and personalized anti-tumor therapy. They further teach that siRNAs have been used for various purposes and have been shown to discriminate between point mutant mRNA targets. Martinez et al do not teach use of nucleic acid modulators such as siRNA (RNAi) to degrade MARK nucleic acid in cells.

However based on the teachings of Drew et al which clearly teach that degradation of MARK polypeptide by PP2A results in reversal of the deleterious phenotypic changes, it would have been obvious to one of ordinary skill in the art to use nucleic acid modulators such as siRNA (RNAi) against MARK in accordance with the teachings of Martinez et al who teaches that it is possible to eliminate or reduce specific nucleic acid molecules in the cell. One of ordinary skill in the art would be motivated to use an siRNA against the MARK nucleic acid because Drew et al clearly teach a link between the deleterious effects of MARK on MAP kinases phosphorylated by MARK. Furthermore one of ordinary skill will be motivated because phosphorylation of the neuronal MAP tau that leads to aggregation of tau proteins in Alzheimer's can be alleviated by eliminating or reducing MARK nucleic acid using a nucleic acid modulator such as an siRNA (RNAi) .

However at the time the instant invention was made it would have been obvious to an ordinary skill in the art to apply a nucleic acid modulator such as an RNAi or PMO against MARK nucleic acid reduce or eliminate the undesirable effects of MARK by preventing its expression or by degrading the MARK nucleic acid which as stated above may lead to microtubule disorganization and cell proliferation or in the case of neurofibrillary tangles that contributes to progression of dementia in Alzheimer's disease.

Arora et al teach that antisense phosphorodiamidate morpholino oligomers (PMO) inhibit targeted gene expression by preventing ribosomal assembly, thus preventing translation. As an example they teach inhibition of cytochrome P450 (P450) 3A4 (CYP3A4) expression in primary human hepatocytes and other cell types using specifically designed PMOs. Arora et al teach that selected PMOs inhibited the expression of CYP3A4 and thus are effective and specific inhibitor of CYP3A4 expression. Thus showing feasibility of using specifically designed PMOs for inhibition of expression to specific genes. Arora et al do not specifically teach using a MARK specific PMO for inhibition of MARK expression in cells.

However, provided the nucleic acid of MARK which was available as of the filing date of the instant invention, one of ordinary skill in the art would have a reasonable expectation success that specifically designed PMOs can inhibit expression of MARK. One of ordinary skill in the art would be motivated to design PMO to prevent expression

of MARK because Drew et al teach that MARK activity towards the MAP kinases result in the deleterious effects discussed above.

Moreover it should be noted that "a reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the method claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion: No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAGNEW H. GEBREYESUS whose telephone number is (571)272-2937. The examiner can normally be reached on 8:30am-5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MANJUNATH RAO can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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